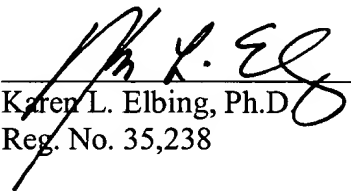


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Respectfully submitted,

Date: 22 March 2002

  
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21559

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ingrid Jochmus et al.	Art Unit:	
Serial No.:	09/980,064	Examiner:	
Filed:	November 29, 2001	Customer No.:	21559
Title:	CYTOTOXIC T-CELL EPITOPES OF THE PAPILLOMAVIRUS L1- PROTEIN AND USE THEREOF IN DIAGNOSTICS AND THERAPY		

Assistant Commissioner For Patents  
Washington, DC 20231

VERSION WITH MARKINGS TO SHOW CHANGES MADE

A marked up version of the amended third full paragraph on page 5 of the specification is presented below.

A functionally active variant of AQIFNKPYW (SEQ ID NO: 1) or AGVDNRECI (SEQ ID NO: 2) means a T-cell epitope which, in a T-cell cytotoxicity assay system (see, for example, Examples 2-5 of the present invention), has a cytotoxicity which, compared to the cytotoxicity of AQIFNKPYW (SEQ ID NO: 1) or AGVDNRECI (SEQ ID NO: 2), corresponds to at least the sum of the average of the negative controls and three times the standard deviation, preferably of at least approx. 30%, in particular at least approx. 50% and particularly preferably of at least approx. 80%.

A marked up version of the amended paragraph beginning on page 5 and ending on page 6 of the specification is presented below.

An example of a preferred variant is a T-cell epitope having a sequence homology to AQIFNKPYW (SEQ ID NO: 1) or AGVDNRECI (SEQ ID NO: 2) of at least approx. 65%, preferably at least approx. 75% and in particular at least approx. 85% at the amino acid level. Other preferred variants are also T-cell epitopes which are structurally homologous to AQIFNKPYW (SEQ ID NO: 1) or AGVDNRECI (SEQ ID NO: 2). Such

epitopes may be found by generating specific T cells against the T-cell epitopes AQIFNKPYW (SEQ ID NO: 1), AGVDNRECI (SEQ ID NO: 2) (DeBruijn M.L. et al. (1991) Eur. J. Immunol. 21, 2963-70; and DeBruijn M.L. (1992) Eur. J. Immunol. 22, 3013-20) and assaying, for example, synthetically produced peptides of choice for recognition by the peptide-specific T cells (see examples). The T-cell epitopes in particular mean cytotoxic T-cell epitopes. However, noncytotoxic T cells are also known which can likewise recognize MHC I molecules so that the present invention also includes noncytotoxic T-cell epitopes as variant.

A marked up version of the amended first full paragraph on page 6 of the specification is presented below.

Another embodiment of the present invention is a T-cell epitope which is part of a compound, the compound not being a naturally occurring L1 protein of a papillomavirus and not being an exclusively N-terminal or exclusively C-terminal deletion mutant of a naturally occurring L1 protein of a papillomavirus. In a particular embodiment, a T-cell epitope having an amino acid sequence AQIFNKPYW (SEQ ID NO: 1), AGVDNRECI (SEQ ID NO: 2), and/or a functionally active variant may be contained in an L1 protein of a different papillomavirus or in a chimeric L1 protein, for example an HPV18L1E7 fusion protein. Such a compound of the invention may have the ability to form CVLPs.

A marked up version of the amended second full paragraph on page 26 of the specification is presented below.

AM peptide means amino acids 366 to 374 of influenza nucleoprotein, sequence: ASNENMETM (see Townsend A.R. et al. (1986) Cell 44, 959-68) (SEQ ID NO: 3).

A marked up version of the amended second paragraph on page 30 of the specification is presented below.

Said three T-cell lines were then assayed in a cytotoxicity assay according to any of the preceding examples for their capability of lysing C3 cells, B6 cells, RMA-S cells and also RMA-S cells which had been loaded beforehand with various L1 peptides (L1-1 to L1-15; concentration in each case 50  $\mu$ M). Fig. 5 shows that T-cell lines 7A and 11C are able to lyse very efficiently L1-14-loaded RMA-S cells. Thus, said T-cell lines are specific for peptide L1-14 which is L1 peptide 330-338 (L1<sub>330-338</sub>). The other assayed peptides were not recognized by said T-cell lines. The sequences of said assayed peptides are as follows: L1-1: GAMDFTTL (SEQ ID NO: 4), L1-2: GDSLFFYL (SEQ ID NO: 5), L1-3: MQVTFIYI (SEQ ID NO: 6), L1-4: VYHIFQFM (SEQ ID NO: 7), L1-5: VHTGFGAM (SEQ ID NO: 8), L1-6: KYPDYIKM (SEQ ID NO: 9), L1-7: VTFIYILV (SEQ ID NO: 10), L1-8: LEDTYRFV (SEQ ID NO: 11), L1-9: GNQLFVTV (SEQ ID NO: 12), L1-10: KKYTFVTV (SEQ ID NO: 13), L1-11: ENDVNYHI (SEQ ID NO: 14),

L1-12: AGVDNRECI (SEQ ID NO: 15), L1-13: TVGENVPDDL (SEQ ID NO: 16),  
L1-14: AQIFNKPYW (SEQ ID NO: 1), L1-15: YKNTNFKEYL (SEQ ID NO: 17)

In the Claims

A marked up version of amended claims 28 and 32 is presented below.

28. (Amended) A T-cell epitope having an amino acid sequence selected from the group consisting of AQIFNKPYW (SEQ ID NO: 1) and AGVDNRECI (SEQ ID NO: 2).
32. (Amended) A T-cell epitope according to claim 29, wherein said variant is structurally homologous to an amino acid sequence selected from the group consisting of AQIFNKPYW (SEQ ID NO: 1) and AGVDNRECI (SEQ ID NO: 2).